Appl. No. : **10/063,569**
Filed : **May 2, 2002**

REMARKS

Claims 4-8 and 11-17 are presented for examination. The specification and claims have not been amended. Applicants respond below to the remaining rejections raised by the Examiner in the Office Action mailed on November 17, 2005.

Rejection under 35 U.S.C. §101 - Utility

The Examiner has rejected Claims 4-8 and 12-17 for the reasons of record and for the additional reasons set forth in the Office Action dated November 17, 2005. The Examiner argues that there is no well-established utility or a disclosed specific and substantial utility. For example, the Examiner continues to argue that being a diagnostic target for melanoma and esophageal tumors is a utility that requires or constitutes carrying out further research to identify or reasonable confirm a "real world" context of use.

In response to Applicants arguments made in the paper filed on August 15, 2005, the Examiner argues that he has not dismissed the differential expression data from Example 18, but that "it is not well-established in the art that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein ... especially in cancerous tissue." The Examiner relies upon Chen et al. (already of record) to support this assertion. Nonetheless, according to the Examiner, even if there were a correlation, "Applicants have still failed to provide a convincing argument that the PRO3566 polypeptide has any relationship at all to cancer" rather than a relationship to "sample age, gender, drug use, smoking normal random distribution, etc." The Examiner asserts that these "confounding variables" are not discussed in the application, and that therefore, any argument regarding relative levels rather than absolute levels of the polypeptide are moot. The Examiner also argues that "the PRO3566 polypeptide has not been shown to be present in different amounts between any normal tissue and its corresponding tumor."

Furthermore, the Examiner states that Applicants' arguments regarding Chen et al. appear to agree with the Examiner's position and that Applicants engaged in "cherry-picking" by focusing on three genes that do show a correlation between mRNA levels and protein levels. According to the Examiner, the "whole thrust" of the experiments of Chen is that a positive correlation between mRNA and protein levels, more likely than not, does not exist.

Finally, the Examiner relies upon Greenbaum et al. ("Comparing protein abundance and mRNA expression levels on a genomic scale," *Genome Biology*, 4:117.1-117.8 (2003)) to support his argument that there is no correlation between mRNA and protein expression. The Examiner states that "Greenbaum et al. teach [that] the knowledge of the amount of an encoding nucleic acid does not automatically bestow the knowledge of the amount of the encoded protein present until considerable further research and experimentation on the significance and function of some biological aspect of the protein is itself performed, which is lacking in the instant application in regards to PRO3566 polypeptides."

Utility – Legal Standard

Applicants again remind the Examiner of the proper legal standard for utility. According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." The Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Also, as Applicants have previously established, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Here, the utility requirement under § 101 is satisfied because: (1) Applicants have provided reliable evidence that mRNA for the PRO3566 polypeptide is more highly expressed in normal skin and esophageal tumor tissue compared to melanoma tumor and normal esophagus tissue, respectively; (2) Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease; and (3) Given Applicants' evidence that the

level of mRNA for the PRO3566 polypeptide is decreased in melanoma tumor and normal esophagus tissue, compared to normal skin and esophageal tumor tissue, respectively, it is likely that the PRO3566 polypeptide is differentially expressed in melanoma and esophageal tumors, and therefore, PRO3566 polypeptides are useful as diagnostic tools to distinguish tumor from normal tissue. The claimed polypeptides thus have utility as diagnostic tools for cancer.

Furthermore, Applicants have established that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true. Again, the standard for establishing an asserted utility is not statistical or absolute certainty.

The specific arguments raised by the Examiner in the Office Action regarding substantial utility are addressed below.

Substantial Utility

The Examiner asserts that the utility of being a diagnostic for melanoma and esophageal tumors is not a substantial utility because it "requires or constitutes carrying out further research to identify or reasonably confirm a 'real world' context of use."

As mentioned above, the Examiner argues that "it is not well-established in the art that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein ... especially in cancerous tissue." The Examiner relies upon Chen et al. (already of record) to support this assertion. Nonetheless, according to the Examiner, even if there were a correlation, "Applicants have still failed to provide a convincing argument that the PRO3566 polypeptide has any relationship at all to cancer" rather than a relationship to "sample age, gender, drug use, smoking normal random distribution, etc." The Examiner asserts that these "confounding variables" are not discussed in the application, and that therefore, any argument regarding relative levels rather than absolute levels of the polypeptide are "moot." The Examiner also argues that "the PRO3566 polypeptide has not been shown to present in different amounts between any normal tissue and its corresponding tumor." Further, the Examiner continues to rely upon Chen et al. and additionally relies upon the newly cited reference Greenbaum et al. to support his position that there is a lack of correlation between mRNA and protein expression between normal and tumor tissue.

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Applicants respectfully disagree with the Examiner's reasoning and submit that the utility of being a diagnostic target for esophageal or melanoma tumors is substantial and specific when the correct utility standard is applied. Applicants again point out that M.P.E.P. § 2107.01 III quotes *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development..." (emphasis added). Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Also, Applicants remind the Examiner that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Here, with regard to the data in Example 18 and the differential expression of the PRO3566 polypeptide, the Examiner is requiring more than is necessary to satisfy the utility requirement. In particular, the Examiner is requiring excessive experimentation, precision and clinical development for the claimed subject matter. The Examiner states that the PRO3566 polypeptide has not been shown to present in different amounts between any normal tissue and its corresponding tumor. Applicants disagree because Applicants have proven that the encoding nucleic acids are differentially expressed in melanoma and esophageal tumor as compared to normal skin and esophagus tissue, and that therefore, it is more likely than not that the encoded polypeptides also are differentially expressed.

This differential expression can be used to distinguish normal skin and esophagus tissue from melanoma and esophageal tumor. Use of the polypeptides or nucleic acids as diagnostics in every melanoma or esophageal tumor diagnosis is not required for utility. As long as the claimed

polypeptides can be used as diagnostics in just one instance, *i.e.*, they are not totally incapable of working at all, then the utility standard under § 101 is met.

Furthermore, in order to have utility as a diagnostic for cancer, a given diagnostic marker need not have a role in causing the cancer. As long as that marker is differentially expressed in that cancer cell compared to the normal cell counterpart, the marker has a utility, regardless of whether it causes the cancer or has some other relationship to the diseased cell. By virtue of being differentially expressed the protein can be used as a marker to diagnose tumor cells.

Also, here the relative levels of mRNA and polypeptide in normal versus tumor cells demonstrates a utility for the claimed subject matter. The "confounding variables" mentioned by the Examiner are not a concern in this case because the manner in which Example 18 was performed. The expression data in Example 18 were made from pooled samples or normal and tumor tissue respectively. Even if a particular cell had expression influenced by one of the Examiner's confounding variables, the pooling of the samples would "wash out" any potential error caused by such variables.

Applicants reiterate that Example 18 in the specification provides sufficient information to establish the utility of PRO3566 nucleic acids, as well as the encoded polypeptides and their binding antibodies. It is not necessary to provide additional information regarding "how high the levels of overexpression are, the nature or number of samples that were used, or about the differences in expression or whether the results were statistically significant." As set forth in the previously submitted "first" Declaration by Grimaldi, "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor." In paragraph 5 of the first Grimaldi Declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 were made from pooled samples of normal and tumor tissues.

Again, an "invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful

product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility."

Applicants next address the Examiner's continued reliance on Chen et al. (hereafter "Chen") to support the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. Also, Applicants address the Examiner's statements that Applicants' previously made arguments support the Examiner's assertions. It appears that the Examiner has not properly understood the previously made arguments and has mischaracterized the discussion of the three genes as "cherry-picking."

Chen provides scant evidence to counter Applicants' asserted utility for the claimed polypeptides because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells or where there is no change in mRNA between samples. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Applicants did not merely "cherry-pick" those genes; those genes were the only one discussed in Chen where there was a difference in mRNA expression. Chen does not provide the data for any of the other samples, and therefore, no conclusions can be drawn as to whether Chen's data are applicable to the instant situation. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value versus protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation

between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression. Chen does not provide contrary data for samples where there was a difference in mRNA levels for a gene. In view of that, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level such that any correlation is masked by imprecision in the measurements. That information is not provided and as a result, it cannot be said that Chen supports the Examiner's position. Only Figure 2 has data where there is a difference in mRNA expression, and for that data, there was a correlation.

Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene.

Finally, Applicants address the Examiner's reliance upon Greenbaum et al. ("Comparing protein abundance and mRNA expression levels on a genomic scale," *Genome Biology*, 4:117.1-117.8 (2003)) for the proposition that there is no significant correlation between mRNA and protein levels. In contrast to the Examiner's position, Applicants argue that Greenbaum demonstrates that, for genes in which the level of mRNA expression varies, there is a high degree of correlation between mRNA and protein levels. In particular, Greenbaum states:

> Logically, we would assume that those ORFs that show a large degree of variation in their expression are controlled at the transcriptional level-the variability of the mRNA expression is indicative of the cell controlling mRNA expression at different points of the cell cycle to achieve the resulting and desired protein levels. Thus we would expect, and we found, a high degree of correlation (r=0.89) between the reference mRNA and protein levels for these particular ORFs; the cell has already put significant energy into dictating the final level of protein through tightly controlling the mRNA expression, and we assume that there would then be minimal control at the protein level.

With respect to genes which do not show variation at the mRNA level, Greenbaum et al. is not relevant because one cannot look at the level of mRNA across several different genes to investigate whether a change in the level of mRNA a particular gene leads to a change in the level of protein for that gene. Furthermore, as discussed above, Applicants are not asserting that transcriptional regulation is the only mechanism for controlling protein levels. Rather,

Applicants maintain that transcriptional regulation is the predominant mechanism for regulating protein levels.

In conclusion, Applicants submit that the utility requirement under § 101 is satisfied because the PRO3566 polypeptide is more likely than not differentially expressed in melanoma and esophageal tumors, and therefore, the claimed polypeptides are useful as diagnostic tools to distinguish tumor from normal tissue.

The Examiner has not offered any significant arguments or evidence to the contrary. Applicants have therefore established a utility for the claimed polypeptides as diagnostic tools for tumors, particularly melanoma and esophageal tumors.

Also, Applicants submit that the Examiner has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. In addition, Applicants submit that the Examiner has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides as diagnostic tools as set forth in the specification. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the utility rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The Examiner has maintained the rejection of Claims 4-5 and 12-17 for lack of enablement arguing that even if the specification were enabling for an isolated polypeptide of SEQ ID NO:64, it does not enable 95% or 99% variants of SEQ ID NO:64. In particular, in the instant Office Action the Examiner argues that Applicant fails to address the Examiner's position that no variant nucleic acid encoding even a single polypeptide variant sharing 95% or 99% sequence identity with PRO3566 has been taught. Also, the Examiner argues that Applicant has provided no teachings or evidence that variants of PRO3566 polypeptide with 95% or 99%

identity are differentially expressed or even exist. Therefore, the Examiner concludes that the claims are not enabled.

Applicants respectfully submit that the claims are enabled because one of skill in the art would know how to make and use the claimed polypeptides. It is not necessary for the specification to have disclosed a particular 95% or 99% variant in order to teach how to make such a variant polypeptide. The amino acid sequence of SEQ ID NO:64 is provided in the specification. One of skill in the art would know how to make isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO: 64. Making variants that differ by 1% or even 5% is well within the skill in the art.

Furthermore, the skilled artisan would know how to identify and make isolated variants which satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal skin and esophageal tumor than in melanoma tumor and normal esophagus, respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal skin and esophageal tumor than in melanoma tumor and normal esophagus, respectively." As previously discussed, Example 18 of the specification teaches how to determine if a molecule is differentially expressed in melanoma tumors or esophageal tumors compared to normal skin or normal esophagus, respectively. One of skill in the art could easily determine if a given variant is differentially expressed and could even engineer a cell that differentially expresses the variant.

Given that it is well known in the art to produce variant polypeptides, and that the specification teaches how to determine the expression pattern, Applicants submit that one of ordinary skill in the art would know how to make and use the sequences according to Claims 4-5 and 12-17.

Likewise, one of skill in the art would know how to make and use isolated polypeptides according to Claims 14-17. The Examiner argues that the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:64 in skin tissue or esophagus tissue samples" is not a functional limitation. The Examiner argues that one of skill in the art would not know how to make a 95% or 99% variant peptide such that antibodies raised against it would recognize SEQ ID NO:64. Again, Applicants disagree.

As discussed above, one of skill in the art can easily make isolated polypeptides that are 95% or 99% identical to SEQ ID NO:64. *See for example*, paragraphs [0256-[0282]. Also, the specification teaches how to make antibodies to the polypeptide of SEQ ID NO: 64. *See for example*, paragraphs [0361]-[0390]. These teachings can be used to generate antibodies against the variant sequences. Thus, one of skill in the art would know how to make and use the claimed polypeptides.

Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

The Examiner also has maintained the rejection of Claims 4-8 and 12-17 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The Examiner continues to argue that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The Examiner has maintained the rejection of Claims 4-5 and 12-17 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. The Examiner argues that the claims have no functional limitations. The Examiner further argues that the claimed sequences may have functions and structures which differ greatly from that of PRO3566. Also, the Examiner asserts that Applicants have argued that mere sequence identity bestows upon the claimed invention all of the function limitations recited in the instant claims.

Applicants respectfully assert that the instant patent application describes the invention in sufficient detail that one of skill in the relevant art could conclude that the inventor was in

possession of the claimed variant sequences at the time the application was filed. Similar to Example 14 of the Written Description Guideline Training Materials, here the specification provides a single species that is representative of the genus because all members have at least 95% structural identity, and the specification provides guidance and teaching on how to identify variants that can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 64 in skin tissue or esophagus samples.

As previously mentioned, a sequence that is a 95% variant will differ from SEQ ID NO:64 by only about 16 amino acids. A 99% variant will differ from SEQ ID NO:64 by only 3-4 amino acids. Thus, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation. One of skill in the art would recognize that Applicants possessed such variants at the time of filing the application based upon the small amount of variation, plus the requirement that the polypeptide can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 64 in skin tissue or esophagus samples.

In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
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> ***
>
> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The Court did not require the Applicants in *Wallach* to actually make and individually describe all of the vast number of sequences which encode the disclosed sequence. This is in spite of the fact that there was no possibility that even the most skilled artisan could "envision the detailed chemical structure of all or a significant number" of encompassed polynucleotides. Because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to describe the very large genus of nucleic acids which could encode the sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO:34, and claim polypeptides which are homologous to it and have the functional limitation of differential expression or the ability to generate antibodies which can be used to specifically detect SEQ ID NO:34 in esophageal or skin tissue samples. It is routine in the art to create polypeptides which have at least 95% or 99% sequence identity to SEQ ID NO:34 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the skill of those in the art to determine which polypeptides share the requisite expression patterns or can be used to make the recited antibodies. These structure/function combinations are sufficient to describe the claimed polypeptides. The *Wallach* opinion makes clear that there is no need to list each individual sequence within the genus to adequately describe the genus.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 64, by specifying a high level of amino acid sequence identity, by describing how to test for differential expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the Examiner reconsider and withdraw the written description rejection under 35 U.S.C. §112.

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Rejection under 35 U.S.C. §102 – Anticipation

The Examiner rejects Claims 14 and 16 as anticipated under 35 U.S.C. § 102(b) by Janer *et al.* (NCBI Accession No. AC006163) (hercinafter Janer; submitted on December 8, 1998). The Examiner argues that nucleic acid sequence disclosed by Janer encodes a polypeptide that is 98% identical to SEQ ID NO:64. The Examiner states that that identity is an inherent feature of the nucleotide sequence disclosed by Janer.

In response to Applicants' previous response, the Examiner has withdrawn the rejection of Claim 4 as anticipated by Janer. However, the Examiner maintains that Janer anticipates Claim 14 due to the recitation in Claim 14 of "wherein said isolated polypeptide or fragment thereof" can be used to generate an antibody. The Examiner argues that the claim language encompasses a fragment of Janer, which fragment would "necessarily and always encode a polypeptide capable of being used to raise antibodies to SEQ ID NO:64.

Applicants respectfully submit that Janer does not anticipate Claims 14 and 16. Janer does not disclose an isolated polypeptide having at least 95% amino acid sequence identity to any of the sequences recited in parts (a), (b) or (c) of Claim 14. Even if the Examiner is correct that Janer encodes a fragment that could generate the specified antibody, that is not enough to anticipate because, as mentioned above, the sequence encoded by the nucleic acid of Janer, the fragment referred to by the Examiner, still fails to meet the other elements of Claim 14.

As previously argued, Janer does not anticipate Claim 14 because it does not disclose an isolated polypeptide. Janer only discloses a nucleic acid sequence. In fact, Janer discloses a sequence with more than 44,000 nucleotides, but it provides no information regarding any isolated polypeptide. Janer does not anticipate parts (a) and (b) of Claim 14 because Janer does not disclose an isolated polypeptide with at least 95% identity to the amino acid sequence of SEQ ID NO:64, with or without its associated signal peptide.

Furthermore, Janer does not anticipate part (c) of Claim 14 because it fails to disclose an isolated polypeptide having at least 95% amino acid sequence identity to ... the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203650. As set forth in Applicants' previous response, the amino acid sequence encoded by the very different nucleotide sequence of Janer sequence has very little identity with the sequence of SEQ ID NO:64. Thus, Janer does not satisfy element (c)

of Claim 14 because it does not disclose the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203650.

Therefore, Janer does not anticipate Claim 14 because it fails to disclose a polypeptide having 95% identity to For these reasons, Janer does not teach a 95% variant according to Claim 14. Because Claim 14 is not anticipated, likewise, Claim 16 cannot be anticipated.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 2/16/06

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